INTELLECTUAL PROPERTY INDIA

सत्यमेव जयते

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

I, the undersigned, being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.* ***961/Del/02*** *dated* ***24th September 2002.***

Witness my hand this 24th Day of October 2003.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

0961-2002

24 SEP 2002

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"A NOVEL PROCESS FOR PREPARATION OF AN ORAL PHARMACEUTICAL COMPOSITION OF FENOFIBRATE "**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. GOWRI SHANKAR MIRIYALA

b. AJAY KUMAR SINGLA

c. SUNILENDU BHUSHAN ROY

d. RAJIV MALIK

of . Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana), INDIA.
Tel. No. (91-124) 6343126; 6342001 – 10; 8912501-10
Fax No. (91-124) 6342027

ORIGINAL

Following declaration was given by the inventors in the convention country:

We, GOWRI SHANKAR MIRIYALA, AJAY KUMAR SINGLA, SUNILENDU BHUSHAN ROY, RAJIV MALIK of Ranbaxy Laboratories Limited, Plot No. 20, Sector 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representative.

a. (GOWRI SHANKAR MIRIYALA)

b. (AJAY KUMAR SINGLA)

c. (SUNILENDU BHUSHAN ROY)

d. (RAJIV MALIK)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

   a. Complete Specification (3 copies)
   b. Drawings (3 copies)
   c. Statement and Undertaking on FORM – 3
   d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **683859** dated **12.08.2002** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **19TH** day of **SEPTEMBER,** 2002.

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
COMPANY SECRETARY

FORM 2

The Patents Act, 1970
(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

ORIGINAL

A NOVEL PROCESS FOR PREPARATION OF AN ORAL PHARMACEUTICAL COMPOSITION OF FENOFIBRATE

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a process of preparing an oral pharmaceutical composition of fenofibrate having an improved dissolution profile.

Fenofibrate, 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester, is useful for the treatment of adult endogenous hyperlipidaemia, hypercholestrolaemia and hypertriglyceridaemia. The usual daily dosage is 67 mg administered in two or three doses or 200 mg once per day.

Fenofibrate is practically insoluble in water and exhibits a low rate of dissolution in aqueous media (including gastrointestinal fluids) that results in inadequate bioavailability after oral ingestion.

Several ways of increasing the rate of dissolution of drugs having low solubility in water have been disclosed in the prior art.

US Patent 4,895,726 assigned to Fournier Innovation et Synergie discloses a fenofibrate composition wherein fenofibrate is co-micronized with a surfactant, in order to improve its solubility. This patent emphasizes that co-micronizing fenofibrate with a solid surfactant improves fenofibrate bioavailability to a much greater extent than either by adding a surfactant to micronized fenofibrate or intimately mixing fenofibrate and surfactant, micronized separately.

In order to further improve the solubility and bioavailability of fenofibrate, Laboratories Fournier in their US Patent 6,074,670 found that this could be achieved by spraying a suspension of the active on a hydro-soluble carrier.

US Patent 6,277,405 also assigned to Laboratories Fournier, SA discloses an immediate release fenofibrate composition comprising an inert hydro-soluble carrier covered with at least one layer containing fenofibrate in a micronized from having a size less than 20 μm, a hydrophilic polymer and optionally a surfactant.

We have unexpectedly found that contrary to the earlier reports, the use of a hydro-soluble carrier is not a prerequisite for improving the bioavailability of fenofibrate and that it is possible to make fenofibrate formulations having improved solubility and bioavailability by spraying a suspension of fenofibrate onto an inert hydro-insoluble carrier. The composition thus obtained was found to posses a release profile similar to that reported in Fournier's US patents 6,074,670 and 6,277,405.

It is an object of the present invention to provide a process for the preparation of a fenofibrate composition comprising layering an inert hydro-insoluble carrier with at least one layer containing fenofibrate in a micronized form, a hydrophilic polymer and a surfactant.

It is a further object of the present invention to provide a process for the preparation of a composition of fenofibrate comprising layering micronized fenofibrate on a hydro-insoluble carrier wherein the composition has a dissolution of at least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using rotating blade method at 75 rpm according to European Pharmacopoeia in a dissolution medium constituted by water with 2% by weight of Polysorbate 80 or with 0.025M sodium lauryl sulphate

It is yet another object of the present invention to disclose a process for preparing a tablet formulation of fenofibrate wherein the micronized fenofibrate, hydrophilic polymer and surfactant are dispersed in water and the dispersion is sprayed onto an inert hydro-insoluble carrier and the granulate thus obtained is mixed with a disintegrant, glidant and lubricant, and compressed to form tablets.

Micronized fenofibrate as described in accordance with this invention has a mean particle size of less than 20 μm. In accordance with another embodiment of the invention the mean particle size is less than 10 μm. The composition comprises from about 20% to about 45% by weight of micronized fenofibrate.

According to this invention, the expression "inert hydro-insoluble carrier" means any pharmaceutically acceptable excipients, water insoluble and inert. Examples of water

insoluble carriers include, but are not limited to, microcrystalline cellulose, dicalcium phosphate, partially pregelatinized starch, and other suitable synthetic and organic polymers.

The hydro-insoluble carrier may be present in an amount from about 20% to about 60% w/w of the total weight of the pharmaceutical composition.

"Hydrophilic polymer", according to this invention should be taken to mean any high molecular weight substance having sufficient affinity towards water. Examples of such polymers include hydroxymethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, gelatin and their mixtures.

The hydrophilic polymer may be present in an amount from about 10% to about 45% w/w of the total weight of the pharmaceutical composition.

A surfactant, according to this invention may be amphoteric, non-ionic, cationic or anionic. Examples of such surfactants are: sodium lauryl sulphate, monoleate, monolaurate, monopalmitate, monostearate or other esters of polyoxyethylene sorbitan, polyethylene glycol laurate, lecithins, propylene glycol alginate, bile acids, phospholipids, propylene glycol laurate, etc. Mixtures of surfactants are also suitable.

The surfactant may be present in an amount from about 0.5% to about 3% by weight of the total weight of the pharmaceutical composition.

The process according to this invention comprises spraying a suspension of active ingredient, in micronized form, and a hydrophilic polymer, onto a hydro-insoluble carrier resulting in a pharmaceutical composition of fenofibrate with improved dissolution profile.

The composition according to this invention can additionally contain other excipients conventionally used in the pharmaceutical and chemical fields which is compatible with the active ingredient, such as disintegrants, glidants, lubricants, binders, fillers, pigments, wetting agents, buffers, etc.

Examples of disintegrants used include those conventionally known in the art, such as croscarmellose sodium, cross-linked polyvinyl pyrrolidone and sodium starch glycolate.

The glidants used in accordance with the present invention include those conventionally known in the art such as starch, talc, stearates and colloidal silica.

Examples of lubricants used in the compositions include stearic acid, talc, magnesium stearate, sodium stearyl fumarate, mineral oil and the like or mixtures thereof.

Examples of binders include those conventionally known in the art such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, gelatin, polyvinyl pyrrolidone and the like.

Examples of fillers used in accordance with the present invention include microcrystalline cellulose, lactose, starch, cross-linked polyvinyl pyrrolidone, etc.

The composition in accordance with the present invention may be filled into capsules, formulated as dry syrups, suspensions or mixed with other pharmaceutically acceptable excipients and compressed to tablets. The tablets may further be coated. Examples of some film forming polymers that can be used for tablet coating are cellulose derivatives (hydroxypropyl methylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose and their derivatives), acrylic and methacrylic copolymers of different molecular weights.

The compositions according to the invention comprise, based on the total composition weight, an inert hydro-insoluble carrier representing 20 to 60% by weight, micronized fenofibrate representing from 20 to 45% by weight, hydrophilic polymer representing from 10 to 45% by weight and the surfactant representing 0.5 to 3% by weight.

Accordingly, the present invention relates to a process for the preparation of an oral pharmaceutical composition of fenofibrate with improved dissolution profile comprising:

a. mixing micronised fenofibrate, 10 to 45 % w/w of a hydrophilic polymer, 0.5 to 5% w/w of a surfactant, to obtain a solution or dispersion, and
b. layering said solution or dispersion on to an inert hydro-insoluble carrier used as 15 to 60% w/w, to obtain granulates,
c. optionally mixing said granulates with pharmaceutically accepted excipients selected from the group consisting of fillers, binders, disintegrants, lubricants, glidants, colourants and flavouring agents, to obtain a mixture,
d. processing said mixture or said granulates as herein described, to obtain said pharmaceutical composition having a dissolution of at least 20% in 10 minutes, at least 50% in 20 minutes and at least 75% in 30 minutes.

The following examples will further exemplify the invention and are not intended to limit the scope of the invention.

EXAMPLE 1

Ingredients	w/w% of composition
Micronized fenofibrate	23
Pregelatinized starch (core)	39.5
Polyvinyl pyrrolidone	17
Sodium lauryl sulphate	1
Microcrystalline cellulose	14
Cross-linked polyvinyl pyrrolidone	4
Colloidal silicon dioxide	0.5
Sodium stearyl fumarate	1

Sodium lauryl sulphate was dissolved in water and the micronized fenofibrate was added to it while stirring continuously. Following this, polyvinylpyrrolidone was added while still agitating to form a dispersion.

The fenofibrate suspension was sprayed onto starch 1500 (partially pregelatinized starch) in Glatt process technology using bottom spray. The granulate thus obtained was mixed with disintegrant, glidant and lubricant and compressed to form tablets. The tablets thus obtained were film coated.

Tablets of this example (I) were compared with Fournier's marketed tablets (II) formulation made in accordance with the invention disclosed in US 6,277,405 for dissolution rate. The rotating blade method (European Pharmacopoeia) is used under the following conditions: volume of medium: 1000 ml; medium temperature: 37^0C; blade rotation speed: 75 rpm; samples taken: every 2.5 minutes. Determination of the amount dissolved is carried out by spectrophotometry. Tests are repeated 6 times over".

Time (Minutes)	% Released	
	I	II
10	86	84
20	100	98
30	101	100

From the results, it is clearly evident that over 95% drug is released in 20 minutes in both the formulations and I and II show substantially similar dissolution profiles. The formulation containing the hydro-insoluble core also gives a dissolution profile similar to that claimed in US 6,277,405.

EXAMPLE 2

Ingredients	w/w% of composition
Micronized fenofibrate	23
Microcrystalline cellulose (core)	39.5
Polyvinyl pyrrolidone	17
Sodium lauryl sulphate	1
Microcrystalline cellulose (extra granular)	14
Cross-polyvinyl pyrrolidone	4
Colloidal silicon dioxide	0.5
Sodium stearyl fumarate	1

Fenofibrate (micronized) suspension was prepared in a similar way as in Example 1 and it was sprayed onto microcrystalline cellulose powder in Glatt process technology using bottom spray. The granulate was mixed with a disintegrant, glidant and lubricant and compressed to form tablets. These tablets were film coated.

Tablets of this example were subjected to dissolution studies using rotating blade method at 50 rpm according to European Pharmacopoeia in a dissolution medium constituted by 1000 ml water containing 0.025M sodium lauryl sulphate.

Time (minutes)	% Released
10	53.0
20	75.1
30	85.2
45	91.0

The results clearly indicate that although the speed was reduced from 75 rpm to 50 rpm, more than 90% of the drug is still released in 45 minutes. Thus, it can be concluded that the formulation containing hydro-insoluble core gives a similar dissolution profile to that claimed in US 6,277,405 even at a slower speed.

The present invention is not limited to the embodiments described. Those skilled in the art will find it apparent that various modifications and variations can be made to the formulations of this invention. Thus, the present invention is intended to cover such modifications and variations, provided they come under the scope of the appended claims.

WE CLAIM:

1. A process for the preparation of an oral pharmaceutical composition of fenofibrate with improved dissolution profile comprising:

    a. mixing micronised fenofibrate, 10 to 45 % w/w of a hydrophilic polymer, 0.5 to 5% w/w of a surfactant, to obtain a solution or dispersion, and
    b. layering said solution or dispersion on to an inert hydro-insoluble carrier used as 15 to 60% w/w, to obtain granulates,
    c. optionally mixing said granulates with pharmaceutically accepted excipients selected from the group consisting of fillers, binders, disintegrants, lubricants, glidants, colourants and flavouring agents, to obtain a mixture,
    d. processing said mixture or said granulates as herein described, to obtain said pharmaceutical composition having a dissolution of at least 20% in 10 minutes, at least 50% in 20 minutes and at least 75% in 30 minutes.

2. The process as claimed in claim 1 wherein the mean particle size of fenofibrate ranges from 10 to 20 microns.
3. The process as claimed in claim 1 wherein said inert hydro-insoluble carrier comprises 20 to 60% w/w.
4. The process as claimed in claim 1 or 3 wherein said inert hydro-insoluble carrier is selected from the group consisting of microcrystalline cellulose, dicalcium phosphate and pregelatinized starch.
5. The process as claimed in claim 1 wherein said hydrophilic polymer is selected from the group consisting of polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl alcohol and gelatin.
6. The process as claimed in claim 1 wherein said surfactant is selected from the group consisting of sodium lauryl sulphate, polyoxyethylene sorbitan esters, sodium monopalmitate, polyethylene glycol laurate, lecithin, propylene glycol alginate, bile acids, phospholipids and propylene glycol laureate.

7. The process as claimed in claim 1 wherein said disintegrant is selected from the group consisting of croscarmellose sodium, crospovidone and sodium starch glycolate.
8. The process as claimed in claim 1 wherein said filler is selected from the group consisting of microcrystalline cellulose, lactose, starch and cross linked polyvinyl pyrrollidone.
9. The process as claimed in claim 1 wherein said binder is selected from the group consisting of hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinylpyrrolidone and gelatin.
10. The process as claimed in claim 1 wherein said glidant is selected from the group consisting of starch, talc, stearates and colloidal silicon dioxide.
11. The process as claimed in claim 1 wherein said lubricant is selected from the group consisting of stearic acid, talc, sodium stearyl fumarate, mineral oil and magnesium stearate.
12. The process as claimed in claim 1 comprising 23 % w/w of fenofibrate having mean particle size of 20 microns, 39.5% w/w of pregelatinized starch, 17% w/w of polyvinylpyrrolidone, 2 % w/w of sodium lauryl sulphate, 14 % w/w of microcrystalline cellulose, 4 % w/w of crosslinked polyvinyl pyrrollidone, 0.5 % w/w of colloidal silicon dioxide and 1 % w/w of sodium stearyl fumarate.
13. The process as claimed in any of claims 1 to 12 wherein said pharmaceutical composition of fenofibrate is obtained as granules, tablets, capsules, dry syrup, suspension or sachets.
14. A process for the preparation of an oral pharmaceutical composition of fenofibrate with improved dissolution profile substantially as herein described and exemplified.

Dated this **19TH** day of **September 2002.**

For Ranbaxy Laboratories Limited

Seal

(Sushil Kumar Patawari)
Company Secretary